ICNIRP/WHO/BfS International Workshop on Risk Factors for Childhood Leukaemia

May 5-7, 2008, Berlin, Germany

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Childhood leukaemia and socioeconomic status

what is the evidence?

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Childhood leukaemia and socio-economic status (SES)

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1. What is socio-economic status (SES)?
2. SES and childhood leukaemia
   - > Existing literature
   - > Methodological problems
3. Current Swiss study
4. Implications for future research

What is SES?

- Common concept in health research, referring to the social and economic factors that influence what positions individuals or groups hold within a society
- Usually, poorer socio-economic circumstances lead to poorer health and higher mortality
- Rare exceptions (breast cancer, melanoma, hayfever?)
- Associations may change over time (lung cancer)

Krieger, Annu Rev Public Health, 1997:18:341-78

Why measure SES?

1. **To describe socio-economic differentials in health**, inform health policy and monitor changes over time
2. **To explain mechanisms** of disease
3. **To adjust for SES as a confounder**, when another exposure is the main focus of interest
   - Many exposures are socially patterned (distance to roads)
   - Use composite indicators, capturing several aspects of SES

Measures of SES

- **No single best indicator** of SES suitable for all study aims, all time points and all settings
- **Each indicator measures different (but related) aspects** that may be relevant to different health outcomes and at different stages in the life course

Galobardes, J Epidemiol Community Health 2006;60:7-12 & 95-101

Measures of SES

Individual level SES indicators

Education

- Knowledge related aspects of a person
- Long-term influence of early life circumstances, adult resources
- Easy to measure, high response rates
- Relevant to all ages and work circumstances
- Meaning varies between birth cohorts (women!)

Galobardes, J Epidemiol Community Health 2006;60:7-12 & 95-101

Measures of SES

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Occupation

- Persons' place in society, social standing, income and intellect
- Social network, stress, autonomy
- Toxic/work task exposures
- Available from routine data (census, death certificates)
- Limitations: unemployed, retired, house workers, students, kids
- Meaning differs between birth cohorts & geographical settings

Galobardes, J Epidemiol Community Health 2006;60:7-12 & 95-101

Measures of SES

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Income

- Material resources (converted into health enhancing commodities and services)
- Dose-response with mortality; accumulates over life
- Can change most at a short-term basis
- Poor response rates, not available in routine data

Housing

- Material aspects of SES
- Easy to collect, or available from routine data
- Specific to period and setting

Galobardes, J Epidemiol Community Health 2006;60:7-12 & 95-101

Measures of SES

Area- level SES indicators

Area-level indicators

- From small-area data, usually from census or other administrative databases
- Proxy for SES of people living in these areas
- Composite scores available (proportion unemployed, with higher education, house and car owners, etc)
- Particularly useful for women and children
- Can change over time

Galobardes, J Epidemiol Community Health 2006;60:7-12 & 95-101

SES and Childhood Leukaemia
Review, Poole et al, IJE, 2006

- Extensive review of literature through August 2002 (N=47)
- Direction of association and p-values
- Results described with regard to
  - study design
  - SES measure (individual or ecological)
  - calendar period
  - geographic locality

Review Poole et al, IJE, 2006
Results 50% : 50%

Negative associations (more leukaemia in deprived families)

- **Case control studies** (control selection bias?)
- **Individual–level measures** (family income, parental education)
- More recent

Positive associations (less leukaemia in deprived families)

- **Registry-based** studies (case selection bias?)
- **Ecological studies with area-based SES measures**
- Older studies

Poole, Int J Epidemiol 2006;35:370-84

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Review Poole et al, IJE, 2006
Recommendations

- **estimate/minimised SES-related selection and participation** in case-control studies
- **compare different SES measures** (which might represent different risk factors
- **consider timing of exposures** (at birth, at diagnosis)
- **evaluate time trends**

Poole, Int J Epidemiol 2006;35:370-84

And then?

?

Quality?

Results?

Poole, Int J Epidemiol 2006;35:370-84

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Recent publications
United Kingdom childhood cancer study

Published by Oxford University Press on behalf of the International Epidemiological Association *International Journal of Epidemiology* 2006;35:1504–1513

doi:10.1093/ije/dyl193

Childhood leukaemia and socioeconomic status: fact or artefact? A report from the United Kingdom childhood cancer study (UKCCS)

Alex Smith,[1]* Eve Roman,[1] Jill Simpson,[1] Pat Ansell,[1] Nicola T Fear[2] and Tim Eden[3]

Accepted 27 July 2006

Background It is widely believed that children of high socioeconomic status (SES) are more likely than those of low SES to develop acute lymphoblastic leukaemia (ALL). Such observations have led to wide-ranging speculations about the potential aetiological role of factors associated with affluence and modernization.

Methods Children (0–14 years) newly diagnosed with cancer in the UK between 1991 and 1996 were ascertained via a rapid hospital-based case finding system (n = 4430, of which 1578 were ALL). Children without cancer (controls) were randomly selected from primary care population registries for comparative purposes (n = 7763). Area-based deprivation scores were assigned as markers of SES at two time points—birth and diagnosis. An individual-based marker of SES—social class—was assigned using father's occupation as recorded on the child's birth certificate.

Results No differences in area-based measures of deprivation were observed between cases and controls at time of diagnosis, either for all cancers combined [n = 4430, odds ratio (OR) = 1.00 (95% confidence intervals (CI) 0.98–1.01)] or for ALL alone (n = 1578 OR = 0.99, 95%CI 0.96–1.01). Findings were similar at time of birth (all cancers, OR = 0.99 95%CI 0.98–1.01, ALL OR = 0.98, 95%CI 0.96–1.00). In addition, no case-control differences were observed when an individual-based measure of SES—social class—based on father's occupation at time of birth was used.

Conclusions The comprehensive nature of the data, coupled with complete case-ascertainment and representative population-based controls suggests that SES in the UK is not a determinant of ALL in children. We believe the small effects reported for SES in some past studies may be artefactual.

Keywords bias, childhood cancer, childhood leukaemia, epidemiology, socioeconomic status

Recent publications
United Kingdom childhood cancer study

- **Case-control study**
- **Cases:** 0-14 yr-olds with leukaemia/all cancers (**1991-96)**
  - **active case finding system**; 10% more than routine registration
- **Controls** from primary care population registries
- **SES measures:**
  - **Area-based deprivation** scores at birth
  - **Area-based deprivation** scores at diagnosis
  - **Paternal occupation** at birth

- No need to contact children for study (data from databases)
- Interviews with cases and controls for other purpose

Smith, Int J Epidemiol 2006;35:1504-13

Recent publications
United Kingdom childhood cancer study

Estimation of potential impact of case and control selection:

- **Analysis I: all selected cases and controls**
  - Whether or not they participated in questionnaire
- **Analysis II: interviewed cases and 1st choice controls**
  - Simulating case selection bias
- **Analysis III: interviewed cases and interviewed controls**
  - Simulating control selection bias

Smith, Int J Epidemiol 2006;35:1504-13

United Kingdom childhood cancer study
Results I **All selected cases & controls**

- Selection bias minimised (all controls, all cases (+10%)
- **No association**
- Results similar for all leukaemias, ALL, all cancers, and paternal occupation

SES quintiles	OR leukaemia (Dg)	OR leukemia (birth)
1 Affluent	1	1
2	1.06 (0.90-1.24)	1.00 (0.85-1.18)
3	0.92 (0.78-1.08)	0.88 (0.74-1.04)
4	1.03(0.88-1.21)	0.96 (0.81-1.13)
5 Deprived	0.96 (0.82-1.13)	0.92 (0.78-1.07)

Smith, Int J Epidemiol 2006;35:1504-13

United Kingdom childhood cancer study
Results II Interviewed cases & first-choice controls

- Simulation of case selection bias
- Only cases participating in interview (595)
- All selected controls
- **spurious protective effect in most deprived group**

SES quintiles	OR leukaemia (Dg)	OR leukemia (birth)
1 Affluent	1	1
2	1.03 (0.86-1.24)	0.92 (0.76-1.12)
3	0.85 (0.71-1.03)	0.75 (0.62-0.91)
4	0.97(0.80-1.17)	0.88 (0.72-1.06)
5 Deprived	**0.80** (0.65-0.98)	**0.77** (0.63-0.94)

Smith, Int J Epidemiol 2006;35:1504-13

United Kingdom childhood cancer study
Results III Interviewed cases & interviewed controls

- Cases refusing interviews excluded (as above)
- Non-responding controls replaced
- Control selection bias >> case selection bias
- **spurious increased risk in most deprived group**

SES quintiles	OR leukaemia (Dg)	OR leukemia (birth)
1 Affluent	1	1
2	1.11 (0.94-1.39)	0.99(0.84-1.18)
3	1.00 (0.84-1.16)	0.90 (0.76-1.07)
4	1.16(0.98-1.37)	1.04 (0.88-1.23)
5 Deprived	**1.21** (1.02-1.43)	**1.08** (0.92-1.28)

Smith, Int J Epidemiol 2006;35:1504-13

United Kingdom childhood cancer study
IV Who moved between birth and diagnosis?

- **50% of families moved** after birth, to more affluent areas
- **Deprived families moved more often**

SES quintiles	OR moving (Dg)
1 Affluent	1
2	1.38 (0.99-1.93)
3	1.15 (1.07-2.12)
4	1.67 (1.19-2.34)
5 Deprived	2.46 (1.75-3.44)

Smith, Int J Epidemiol 2006;35:1504-13

Recent publications

Population mixing, socioeconomic status and incidence of childhood acute lymphoblastic leukaemia in England and Wales: analysis by census ward

CA Stiller*[,1], ME Kroll[1], PJ Boyle[2] and Z Feng[2]

[1]*Childhood Cancer Research Group, Department of Paediatrics, University of Oxford, Oxford OX2 6HJUK, UK;* [2]*School of Geography and Geosciences, Irvine Building, University of St Andrews, St Andrews KY16 9AL, UK*

In this population-based study of acute lymphoblastic leukaemia (ALL) diagnosed among children aged under 15 years in England and Wales during 1986–1995, we analysed incidence at census ward level in relation to a range of variables from the 1991 census, which could be relevant to theories of infectious aetiology. 'Population-mixing' measures, used as surrogates for quantity and diversity of infections entering the community, were calculated from census data on the origins and destinations of migrants in the year before the census. Incidence at ages 1–4 years tended independently to be higher in rural wards, to increase with the diversity of origin wards from which in-migrants had moved during the year before the census, and to be lower in the most deprived areas as categorised by the Carstairs index. This last association was much weaker when urban/rural status and in-migrants' diversity were allowed for. There was no evidence of association with population mixing or deprivation for ALL diagnosed at ages 0 or 5–14 years. The apparent specificity to the young childhood age group suggests that these associations are particularly marked for precursor B-cell ALL, with the disease more likely to occur when delayed exposure to infection leads to increased immunological stress, as predicted by Greaves. The association with diversity of incomers, especially in rural areas, is also consistent with the higher incidence of leukaemia predicted by Kinlen, where population mixing results in below average herd immunity to an infectious agent.

British Journal of Cancer (2008) **98,** 1006–1011. doi:10.1038/sj.bjc.6604237 www.bjcancer.com
Published online 5 February 2008

Keywords: leukaemia; child; population mixing; urbanisation; deprivation; population density

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Recent publications

B) **Population mixing, socio-economic status and incidence of ALL in England and Wales**

- **Cohort study**
- **Cases:** children with ALL diagnosed 1986-95 at age 0-14 yrs from population-based National Registry of Childhood Tumours
- **Person-years at risk from 1991 census (x10)**
- **SES measure:**
  - **Carstairs deprivation score** (ward level),
- Poisson regression

Stiller, British J of Cancer 2008:98:1006-11

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B) Population mixing, socio-economic status and incidence of ALL in England and Wales

Results (for 1-4 year olds only)

- no control selection bias
- Cancer registry cases (-10%); case selection bias?
- **Small protective effect in most deprived group**
- *Adjustment for urban/rural and diversity of incomers

SES quintiles	OR ALL at Dg (crude)	OR ALL at Dg (adj*)
1 Affluent	1	1
2	0.01	1.02
3	0.99	1.01
4	0.94	0.99
5 Deprived	**0.82** (p= 0.011)	**0.87** (p=0.007)

Stiller, British J of Cancer 2008:98:1006-11

Recent publications

C) **Childhood Leukaemia & SES in Canada**

ORIGINAL ARTICLE

Childhood Leukemia and Socioeconomic Status in Canada

Marilyn J. Borugian,[*] John J. Spinelli,[*] Gabor Mezei,[†] Russell Wilkins,[‡] Zenaida Abanto,[*] and Mary L. McBride[*]

Background: Leukemia is one of the most common potentially fatal illnesses in children, and its causes are not well understood. Although socioeconomic status (SES) has been related to leukemia in some studies, this apparent association may be attributable to ascertainment or participation bias. This study was undertaken to determine whether there is a difference in incidence of childhood leukemia for different levels of SES, as measured by neighborhood income, in an unselected population case group.

Methods: All cases of childhood leukemia diagnosed in the years 1985–2001 were identified from population-based cancer registries in Canada. Postal codes for the place of residence at diagnosis were used to ascertain the census neighborhoods for cases. We constructed neighborhood-based income quintiles from census population data, and stratified the population at risk by sex and 5-year age groupings. Age-standardized incidence rates and 95% confidence intervals (CIs) were calculated. We used Poisson regression to other studies may be related to differences in case ascertainment or study participation.

(*Epidemiology* 2005;16: 526–531)

Early studies of childhood leukemia have reported a higher incidence with higher socioeconomic status (SES).[1–3] In more recent case–control studies of extremely low-frequency magnetic fields and childhood leukemia, however, cases tended to be of lower SES than controls, suggesting a possible inverse association between SES and childhood leukemia.[4–6]

The inverse association observed in these recent epidemiologic studies may represent a real association between SES and childhood leukemia, which may have shifted over time from the previously observed positive association. If this shift is real

Borugian, Epidemiology 2005;16:526-31

Recent publications

C) **Childhood Leukaemia & SES in Canada**

- **Cohort study**
- **Cases:** all children with leukaemia diagnosed 1985 -2001 from population-based cancer registries in Canada
- **Person-years at risk from census data**
- **SES: area-based income quintiles** (census data)
- Poisson regression
- Time trends

Borugian, Epidemiology 2005;16:526-31

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C) Childhood Leukaemia & SES in Canada

Results

- no control selection bias
- Cases from cancer registries; case selection bias possible?
- **small protective effect in most deprived group**
- **no time trends**

SES quintiles	OR all leukaemias (Dg)
1 Affluent	1
2	0.92 (0.84-1.00)
3	0.97 (0.89-1.05)
4	0.96 (0.88-1.04)
5 Deprived	**0.87** (0.80-0.95)

Smith, Int J Epidemiol 2006;35:1504-13

Taylor & Francis
healthsciences

Socioeconomic status and risk of childhood leukaemia in Denmark

Ole Raaschou-Nielsen, Josephine Obel, Susanne Dalton, Anne Tjønneland and Johnni Hansen

Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

Scand J Public Health 2004; 32: 279–286

Aims: The aim of this study was to assess the influence of socioeconomic status on the risk of childhood leukaemia. *Methods*: A matched case-control design was used. The study population comprised all children (0–14 years old) born and reported to the Danish Cancer Registry between 1976 and 1991 for a diagnosis of leukaemia ($n=377$). Controls were selected from the Central Population Registry and matched by sex, age, and time of birth. Each child was assigned three categories of socioeconomic status, one corresponding to the annual average income in the municipality of residence at the time of birth, another corresponding to that at the time of diagnosis, and, finally, each family was assigned one of five social classes by use of the job titles of the parents. Conditional logistic regression was used to estimate the effect of socioeconomic status on the risk of childhood leukaemia. *Results*: Children born in low-income municipalities had a significantly increased risk of leukaemia (RR = 2.71; 95% CI = 1.41–5.21; $p=0.003$), which was higher among those who received their diagnosis before age five (RR = 3.43; 95% CI = 1.52–7.74; $p=0.003$). Neither individual social class nor the socioeconomic status of the residential area at the time of diagnosis was convincingly associated with the risk of childhood leukaemia. *Conclusions*: The results suggest that socioeconomic factors associated with community characteristics rather than individual lifestyle are related to the risk of childhood leukaemia and that these factors act early in life.

Key words: childhood, leukaemia, social class, socioeconomic status.

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Recent publications

D) **SES and risk of childhood leukaemia in Denmark**

- **Matched case-control study**
- **Cases: all** children aged 0-14 years with leukaemia reported from 1976-91 to the Danish Cancer Registry
- **Controls from Central Population Registry,** matched for age, sex and time of birth
- **SES measures:**
  - municipality income at birth and at diagnosis,
  - parental occupation
- Conditional logistic regression, time trends
- Adjustment for maternal age, birth order, housing, urbanisation, geographic region (no changes in OR)

Raaschou-Nielsen, Scand J Public Health 2004:32:279-86

D) SES & risk of childhood leukaemia in Denmark

Results

- **Increased risk** for children **born in poor municipalities**
- No association with income at Dg or parents occupation
- No time trends
- Stronger risk in 1-4-year olds, stronger for AML

	Municipality (birth) OR	Municipality (Dg) OR
1 Affluent 10%	0.81	0.89
2 Medium 80%	1	1
3 Deprived 10%	**2.71**(p= 0.003)	0.97

Raaschou-Nielsen, Scand J Public Health 2004:32:279-86

SES & Childhood Leukaemia in Switzerland

Adam, Zwahlen, Egger, Kuehni

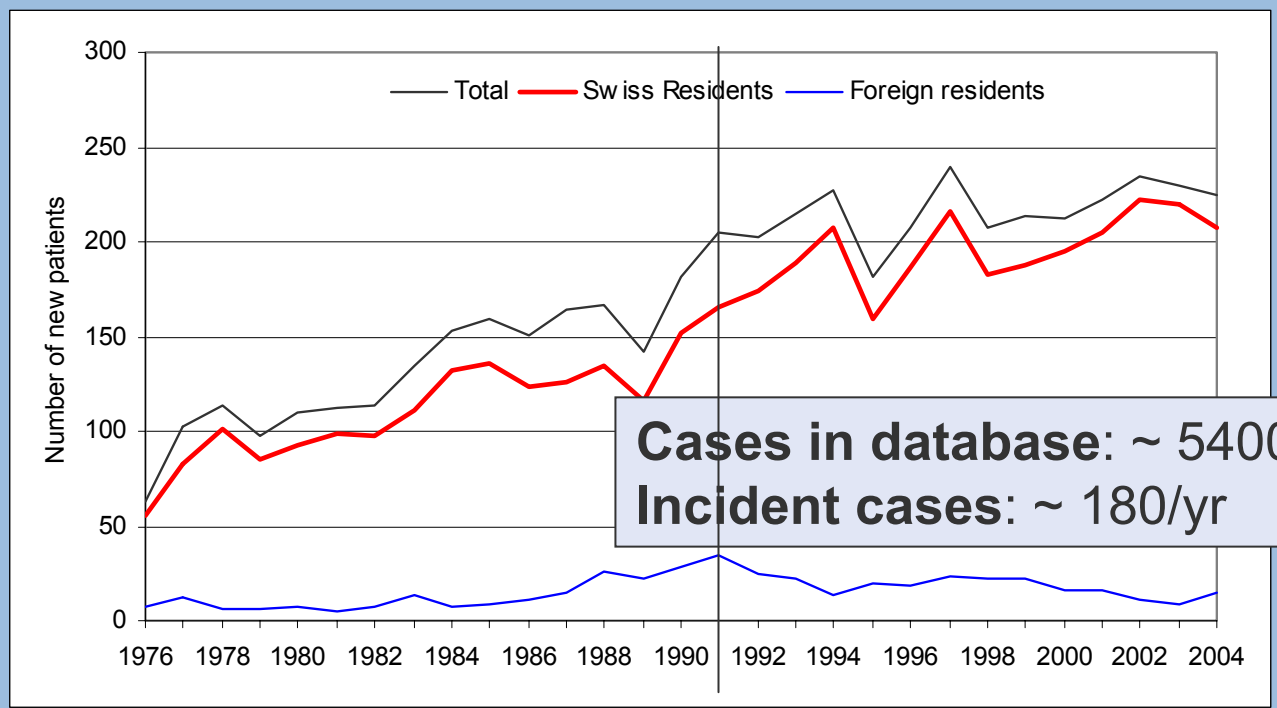
Study design

- Case control (case cohort) study
- Linkage study between
  - Swiss Childhood Cancer Registry (Cases)
  - Swiss National Cohort (Controls, 4 per case)

SES & Childhood Leukaemia in Switzerland

Cases: The Swiss Childhood Cancer Registry

- National childhood cancer registry, founded 1976
- since 1990ies: incidence ~ Germany/France/UK



- **Inclusion:**
- all cases born before 1990 (2000) census and diagnosed after census (1991-2007):

~700 leukaemias

Michel & Kuehni, Swiss Med Wkly 2007:137:502-5

Controls: The Swiss National Cohort (SNC)
National cohort study of 6.874 million people

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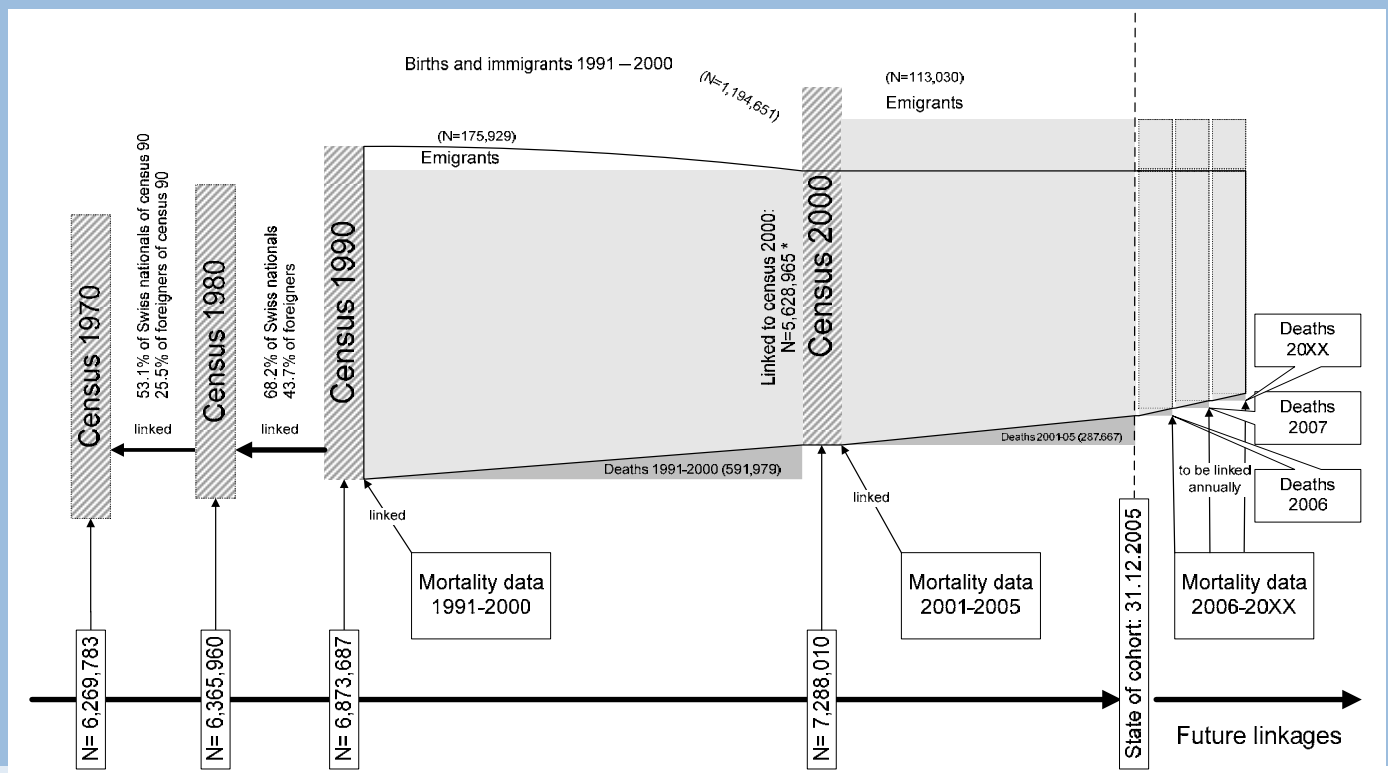
> Linkage of anonymous records: **Census data** (1990 + 2000), **mortality & migration records** (ongoing)



* 476,814 individuals could not be linked to the census 2000, a mortality or emigration record (see table 2).

> **93% linked**

SES & Childhood Leukaemia in Switzerland

Controls: The Swiss National Cohort (SNC)

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- **4 controls per case drawn from SNC**
- **Frequency matched for year of birth, same census**
- **Various SES measures** (prior to diagnosis)
  - Parental education and occupation
  - Housing (no of persons/rooms, ownership, rent)
  - Area-based measures (SOTOMO index)
    - at time of birth
    - at time of census

Bopp et al, Int J Epidemiol, 2007:epub

SES & Childhood Leukaemia in Switzerland

Strengths & limitations

- No control selection bias
- No/little case selection bias
- Exposures assessed before diagnosis
- Several family-based and area-based SES measures
- Cultural diversity (French vs. German speaking areas)
- Time trends
- Power: 90% power to assess of OR of 1.3 to 1.5

SES & Childhood Leukaemia in Switzerland

Results

>**Next year**

Leukaemia and socio-economic status **Summary**

- **Results heterogeneous**, **~50% suggesting a positive, 50% a negative association**
- **small effects** (in both directions),
- **mostly affecting extreme SES groups** (10-20% most/least deprived)
- **Area-based measures**, and **exposure early in life** might be more relevant
- **Results very sensitive to control and case selection bias**
- **Unlikely to be a strong confounder**

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Leukaemia and socio-economic status
Future studies should

- **Avoid case and control selection bias**
- **Distinguish**
  - different SES measures
  - time points of exposure
  - age groups and cancer subtypes
  - time trends
- **Compare results between studies/countries**
  - Reanalyse existing data with approaches of studies with opposite results
- **Interpret findings** (mechanisms)

Acknowledgments

ISPM, University of Bern, Switzerland

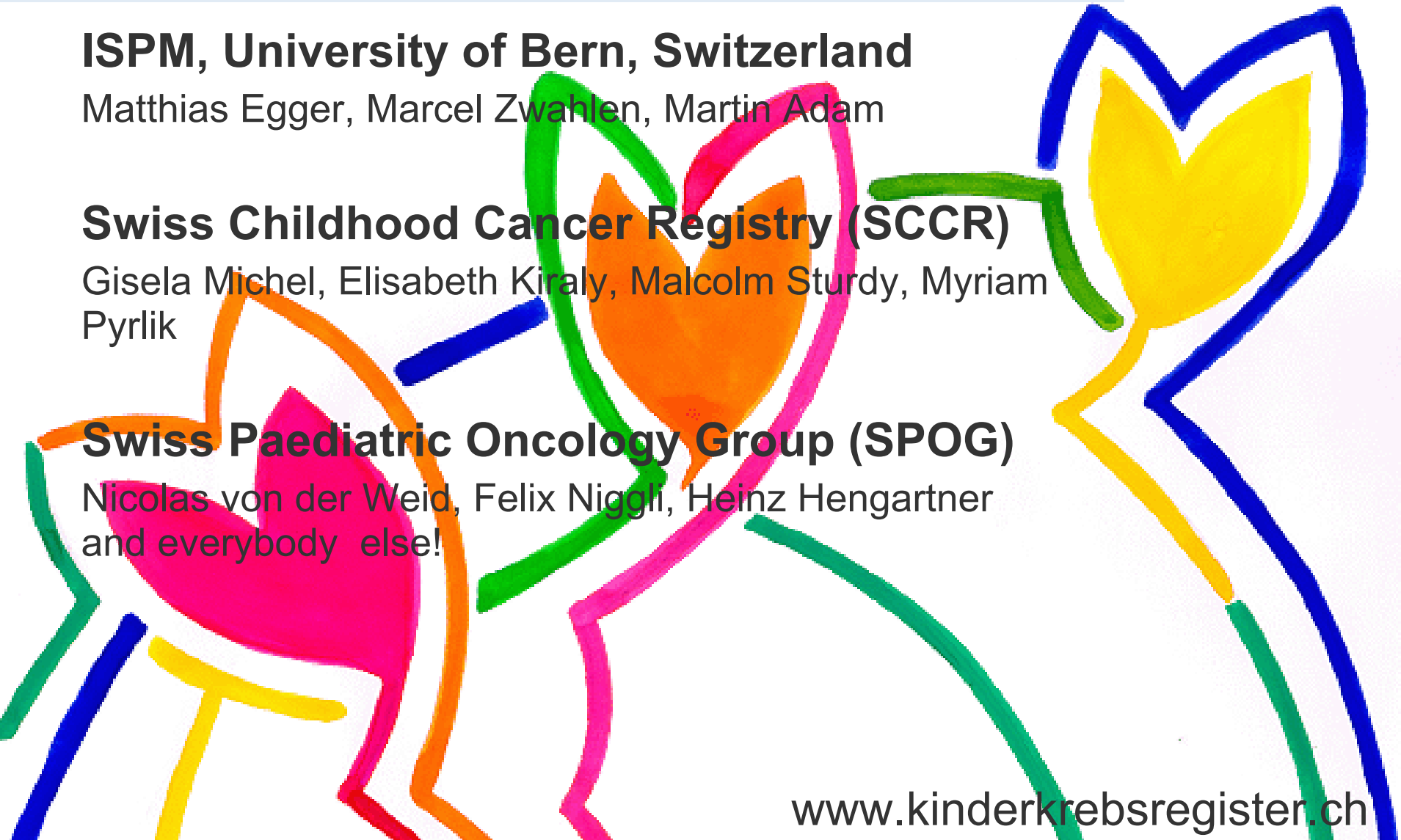
Matthias Egger, Marcel Zwahlen, Martin Adam

Swiss Childhood Cancer Registry (SCCR)

Gisela Michel, Elisabeth Kiraly, Malcolm Sturdy, Myriam Pyrlik

Swiss Paediatric Oncology Group (SPOG)

Nicolas von der Weid, Felix Niggli, Heinz Hengartner and everybody else!



www.kinderkrebsregister.ch

SES & Childhood Leukaemia in Switzerland SOTOMO Index

- **1. Index: Social status**
  - Net income, education level and job position
- **2. Index: Individualised lifestyle**
  - Living alone, working mother
- **3. Index: Integration and language barrier**
  - Proportion not speaking local language
- **4. Index: Population aging**
  - Proportion of children, working and elderly

Information from the SNC

- **Information on individuals**: sex, date of birth, place of birth, nationality, place of residence now, residence 5 years ago, educational level, occupation, employment status
- **Household information**: no of rooms, no of persons, surface area, owned or rented, rent per month
- **Building characteristics** (geographical coordinates)